

Moral assessment of growth hormone therapy for children with idiopathic short stature

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Abstract

The prescription of growth hormone therapy for children who are not growth hormone deficient is one of the controversies in contemporary paediatric endocrinology. Is it morally appropriate to enhance the growth, by means of medical treatment, of a child with idiopathic short stature? The medical, moral, and philosophical questions in this area are many. Data on the effects of human growth hormone (hGH) treatment will not on their own provide us with answers, as these effects have to be evaluated from a normative perspective. In this article we consider hGH treatment for children of idiopathic short stature from three normative perspectives: the goals of medicine, the good of the patient, and the public good. We argue that the prevention of psychological and social problems due to short stature (and not merely the enhancement of growth) should be the ultimate goal of medical treatment and research.

Introduction

The controversy around expanded use of human Growth Hormone (hGH) has arisen since it became possible to produce hGH by recombinant DNA technology.¹ Before biosynthetic hGH became available in 1985, children were treated with natural growth hormone, extracted in very small amounts from the pituitary glands of cadavers. Given the limited supply of growth hormone, it was considered evident that only patients with established growth hormone deficiency should be treated with this hormone. Moreover, the criteria used to define growth hormone deficiency were rather restrictive.²

Now that the supply of synthetic hGH is – at least technically – unlimited, this situation has changed. It appears no longer necessary to restrict treatment to undisputed cases of growth hormone deficiency. First, the availability of hGH has led to a relaxation of criteria defining GH-insufficiency.³ Second, since hGH became available in larger quantities, growth

hormone has been prescribed for children with short stature that is not caused by growth hormone deficiency but other conditions such as Turner's syndrome and renal failure.

In this paper we will concentrate on the treatment of children with idiopathic short stature. Idiopathic short stature implies that there is not (yet) a specific dysfunction diagnosed as the cause of abnormal growth. The question arises whether it is morally appropriate that physicians give medical treatment to people who do not have a diagnosed disease: is the administration of growth hormone for idiopathic short children morally justifiable?

Evaluation of effectiveness of hGH therapy

Many discussions on the acceptability of growth hormone treatment for children without established growth hormone deficiency focus on the *effectiveness* of the intervention. Growth hormone therapy may stimulate growth. North American and European trials have demonstrated that hGH therapy improves growth velocity for at least a period of three years.⁴ For example, in a study by the US Genentech Collaborative Study Group, which included children between five and ten years of age with 2.5 standard deviations below average height, the mean growth velocity increased from 4.6 cm/year to 8.0, 7.6, and 7.2 cm/year in the first three treatment years. Predicted adult height improved from -2.7 to -1.6 standard deviations from the mean.⁵

The effects of hGH on final height are less clear, as most studies do not include an untreated control group. Notably, the inclusion of placebo controls is generally deemed morally inadmissible.⁶ Furthermore, the acceleration of puberty caused by growth hormone therapy results in an extra advancement of skeletal age, which has a negative effect on final height. In a study by the Dutch Growth Hormone Working Group the final height of 12 GH-treated idiopathic short subjects has been compared to the final height of untreated "retrospective" controls. Final height of the hGH-treated children (159.2 ± 8.0 cm, or -2.6 ± 1.0 SDS) turned out to be similar to that of untreated controls.⁷ On the basis of such outcomes, some would consider hGH

Key words

Ethics, medical; growth-disorders drug therapy; endocrinology; philosophy, medical; growth hormone therapy; children with idiopathic short stature.

treatment inappropriate for children with idiopathic short stature. On the other hand, some researchers in endocrinology conceive of these outcomes as reasons for further research. They suggest that the effectiveness of hGH therapy could be improved by refining the criteria for responsiveness to growth hormone. Furthermore, by combining hGH therapy with hormone treatment which will delay the onset of puberty, the final height of children could be further enhanced.⁷ So, ongoing endocrinological research may result in an improved efficacy of hGH therapy for at least specific groups of children with idiopathic short stature.

But if the effectiveness of hGH-therapy can be improved for some children with idiopathic short stature, does this imply that such therapy is morally justified? Data on effects of a therapy do not as such provide doctors and scientists with practical directives. The established fact that a drug has certain effects in some people does not imply the ethical conclusion that the prescription of that drug for those people is morally appropriate. Effects must be evaluated from a normative perspective in order to imply practical conclusions for clinical medicine. In the context of the physician-patient relationship, the dominant moral value is the individual patient's good. Effects will be assessed as possible benefits and harms for the patient concerned. For a large part this evaluation is to be made by the patient him/herself. Nevertheless, this patient-related perspective cannot provide the sole basis for answering the question whether it is appropriate to offer treatment to a whole group of people. Even more, one patient's assessment cannot answer the question whether refinement of growth hormone therapy for idiopathic short stature is important enough for the advancement of medical science and practice to merit experimental treatment. Here the goals of medicine itself are at stake. Certainly, the individual patient's assessment has little or no bearing on the question whether idiopathic short stature is at all to be considered a medical condition in need of medical intervention. Probably, it is not just one's short stature which may cause suffering, but society's negative attitudes towards short people. Before medicalising a social problem, we should evaluate whether such medicalization fits our ideals of a good society. In the next three sections, the justifiability of hGH treatment will be addressed from these three normative perspectives: the goals of medicine, the patient's good and the good of society.

hGH therapy and the goals of medicine

Do the objectives of hormone therapy fit in with the overall goals of medical science and health care practice? What are these overall objectives anyway? Some caution is warranted here. One should not have the illusion that the goals of medical science and practice may be easily circumscribed. Further-

more, if it is possible to describe or to define objectives of medicine, these will be constantly put into question by new technologies and possibilities. Incoherence between accepted goals and actual practice should serve as a starting point for critical medico-philosophical and ethical reflection. This may not only lead to adjustment of practice, but also to adjustment of the overall goals.

Theoretical perspectives

A rather general description is that medicine aims at the prevention and elimination of disease, the relief of suffering due to disease and the restoration of health. Whether the goal of hGH therapy for children with idiopathic short stature fits this overall objective depends on whether idiopathic short stature is a disease and whether growth enhancement fosters health. But there are diverse theoretical perspectives on the concepts of health and disease. One may distinguish analytical and holistic perspectives on health and disease.⁸ Analytical theories take "disease" to be the basic concept, and they define health in terms of (absence of) disease. For example, Boorse's biostatistical theory considers disease to be an internal state that interferes with (biostatistical) normal functions of organs or mental faculties.⁹ In a holistic theory, on the other hand, health is viewed as the basic concept and disease is defined in terms of health, that is, a disease is a bodily or mental process which tends to compromise health. In Nordenfelt's holistic theory, health is defined as the ability of a person to realise under standard circumstances all the goals necessary for his minimal happiness.¹⁰

Notwithstanding the significant differences between both perspectives on the nature of health and disease, it is difficult to count idiopathic short stature as a disease in either of these two views. As mentioned, from the perspective of (analytical) biostatistical theory, a condition is called a disease if an organ's function is subnormal:

"Whether a man is healthy or diseased . . . is a completely objective affair. The tasks are to find the specific goals of the bodily organs and mental faculties, to calculate the average contribution of these organs in the attainment of the goals, and to study whether a particular organ fulfils this average requirement."¹¹

Though bodily length of persons with idiopathic short stature is far below average levels, the condition is characterised by the absence of knowledge of biostatistical subfunctioning *organs*. A person's short stature may simply be considered as fitting within a broader defined normal variance in stature within a population. As long as no subnormal functioning bodily organs or mental faculties have been discovered, the term "disease" seems to be inappropriate from a biostatistical perspective.

In Nordenfelt's holistic approach, idiopathic short stature counts as a disease if it tends to compromise health, that is, a person's ability to realise minimal happiness. Recent psychological research shows that very short adolescents and adults have a significantly greater risk for psychological, cognitive and sexual problems.^{12 13} These problems related to short stature may indeed lead to a person being unable to realise minimal happiness. But these observations also shift the attention from the limited growth as such to the mental and psychosocial consequences of short stature. Rather than shortness being a disease in need of hGH therapy, the correlated psychological, cognitive, and sexual risks call for appropriate preventive intervention. Obviously, it is not clear whether hGH qualifies as the appropriate therapy.

These theoretical disputes are mirrored by the practical controversy among endocrinologists about when to prescribe growth hormone. One group of physicians, sometimes labelled as "traditionalists", holds to diagnostic criteria of growth hormone deficiency, based on threshold blood levels of growth hormone. In this approach the diagnosed disease, defined as abnormal functioning of bodily organs, is central.¹⁴ These "traditionalists" face the problem that there are no highly specific and sensitive diagnostic tests for growth hormone deficiency. Others emphasise that indications for prescription of hGH therapy should be determined by criteria such as the severity of *disability* resulting from short stature, the expectation of psychosocial and/or functional benefit, and proven responsiveness to therapy.³ Though disability due to short stature implicitly may have been the major target for hGH therapy, this has not yet been manifested in consensus on prescription criteria, nor has it directed the focus of medical research to the (psychosocial) consequences of short stature.

Ultimate objective

If it is accepted that the ultimate objective of growth hormone treatment is to reduce the risk of psychosocial disability, and that the objective of enhancing growth is a means to that goal, then hGH therapy may fit the formulation of the goals of medicine provided earlier. But evidently, the next question will be whether hGH treatment is the most appropriate means to that end. Consequently, medical research with hGH treatment should focus on the effects on psychological wellbeing rather than on growth as such. Even more importantly, scientists should study whether psychological problems may be better addressed and prevented by psychological interventions and support.

Within the context of clinical practice, the intermediate conclusion can be that, if growth hormone therapy is considered as a means to reduce the risks of mental and social problems, then these aspects of

wellbeing also need to be explicitly looked at. For that reason, hGH treatment of small persons should not be an isolated therapy, but should be combined with psychological care and counselling.

hGH and the patient's good

If hGH therapy is considered as an appropriate medical intervention, which fits the objectives of medicine and health care, a crucial question will become whether this therapy serves the individual patient's good. In order to answer this question, effects must be assessed in terms of harms and benefits for the patient.

Possible benefits of growth hormone therapy include a chance of extra growth and perhaps a reduced risk for psychological problems. The burdens of treatment concern daily injections for a period of several years. The impact of daily invasive treatment on a young child and on family life should not be underestimated. There is a possibility that such a treatment may induce psychological problems. The child who realises that the daily injections are for the sake of growth, may develop a strong conviction that normal stature is extremely important. As the effects of treatment are limited, there is a chance that the child will suffer from a large discrepancy between her ideal and her actual stature. On the other hand, the risks of physical harm caused by hGH treatment, appear to be remarkably small.^{14 15} Most serious is a reported increase in incidence of leukaemia during hGH treatment of GH-deficient patients. Boose *et al* found a higher incidence of leukaemia in the population of children treated with GH (5:100,000) than in the age-related normal population of children (2:100,000), but strong evidence that GH therapy may induce leukaemia has not yet been found.¹⁶

How should these benefits and harms be weighed? As people have divergent views on the evaluation of risk, pain, health and medicine, the patient's own perspective is most relevant for weighing her benefits and harms. Probably, for many people the benefits of growth hormone treatment will not weigh up to the trouble it involves. For example, one person may focus on the prevention of disability in psychological functioning and he may think that the chances of effective prevention by growth hormone therapy are remote. But another person may focus on the growth as such, and give less weight to the psychological issue. For her, growth may be one of the most important issues in her life, and she may accept going through a lot of trouble in order to increase the chance to improve growth, even if she will gain only a few extra centimetres. Furthermore, for many people it is important that they have tried every option which may ameliorate their condition. So, even if in the end the results of treatment are disappointing, a person may be glad she has taken the

opportunity of growth hormone treatment – or at least she may still be convinced that her choice for treatment was a good choice. Consequently, considered from the perspective of the patient's own good, hGH treatment may well be evaluated as acceptable in individual cases. Even if the medical value of hGH therapy is controversial, a patient may come to the conclusion that the burdens of growth hormone therapy are not overly heavy. The physician has the obligation to explain possible effects and side effects, in order to enable the patient to come to an autonomous choice.

However, in many cases of idiopathic short stature the patient's perspective on her own good will be difficult to grasp. Often, the children involved will only be six years of age. In those and other cases it is not the children themselves but their parents who seek treatment. Naturally, if the parents weigh the benefits and harms of growth hormone therapy, they will be led by their own ideals of how a child should be. But the ideal picture parents have of their child does not necessarily represent the best interests of this child, if only because many children end up not fulfilling their parents' ideal picture.

Is a proxy consent of the parents in this context a sufficient substitute for an autonomous decision of the patient herself? We think that proxy consent can be sufficient if the physician agrees with the parents that hGH therapy could be beneficial to the child, and if he is certain that the parents' expectations of the therapy are reasonable. Therefore, it is important that doctor as well as parents focus on the child's overall wellbeing rather than on growth alone.

Above all, the child's own assessment of the therapy and its goals should not too easily be overlooked. Even though many children of five or six years of age will not be able to grasp and evaluate all relevant consequences of a decision to accept or forgo treatment, parents and physician may get an idea to what extent the child considers its short stature to be a problem. Furthermore, if treatment is started, the child's evaluation of the burdens of therapy can and should be carefully monitored. If the child considers the daily injection as burdensome, then doctor and parents have a good reason to stop hGH treatment.

hGH therapy and the good of society

A third normative framework for evaluating the appropriateness of growth hormone therapy for children with idiopathic short stature concerns the public good. At least three types of moral considerations are relevant: considerations of justice, of medicalization and of stigmatisation.

First, there is the question of allocation of resources. Expanded use of growth hormone implies expanded costs for health care. Growth hormone

therapy for a child with idiopathic short stature takes several years, the treatment is expensive and the effectiveness in terms of predicted adult height is minimal. Even when new techniques enhance the effectiveness of hGH therapy, one should face the question whether growth hormone therapy for children of idiopathic short stature can be morally justified in times of scarce health care resources.¹⁷ We will not elaborate this problem further, as we think that the problem of justice should not be dealt with before the moral acceptability of the therapy itself has been determined.

Medicalization

A second concern is that expanded use of growth hormone may result in a medicalization of the phenomenon of short stature. Medicalization can be defined as the social process wherein medical terms become relevant for more and more phenomena of daily life.¹⁸ Medicalization processes may be criticised from a moral point of view when they result in a growing dependence of groups of people on the medical professions. Medicalization turns people into patients. This is not necessarily a problem for the individual short person who is asking for medical care. But a society which holds autonomy and independence as important ideals, may be cautious in declaring a physical condition a disease if it does not necessarily result in suffering. Nevertheless, moral objections to medicalization become less relevant in cases where the interventions aim at a reduction of psychological and social risks of short stature, rather than at enhancement of growth as such. After all, these risks are not trivial, and medical and psychological interventions may have beneficial effects for the persons concerned.

However, from the perspective of a good society, the emphasis on psychological and social wellbeing of short persons is not without moral problems either. One may argue that the psychological and social problems concerned will at least in part be caused by the societal prejudices concerning short stature. Short people are easily overlooked – in the literal and figurative sense. They may be stigmatised as abnormal and unimportant. Adults of 150 cm height are constantly confronted with the fact that the physical and social world in which they live is not adapted to people of their length. If their problems are indeed caused by social factors, then one may argue that interventions should not be directed at the short people, but first of all at society. As long as interventions focus on short people and not on society, the cultural stigma of shortness being abnormal and problematic, is reinforced.

In our opinion, these considerations offer highly important reasons for public policies and private initiatives against social prejudice, but they do not

justify abstaining from medical care for the individual persons concerned. First of all, short people may find more concrete benefit in medical and psychological care than in public attempts to change social attitudes. For that reason, secondly, the parents of short children should not be morally blamed if they choose medical treatment in the hope of reducing certain risks, rather than heroically offering resistance to society's prejudices. Finally, if a physician is confronted with parents who worry about the wellbeing of their small child, he ought to concentrate on the wellbeing of this concrete patient. The battle against social prejudice is important, but it is, in this context, not the primary obligation of the physician.

Conclusion

Is the administration of hGH for children with idiopathic short stature morally justified? If the goal of this therapy is simply to *enhance bodily stature* then this question should be answered negatively from both the medical perspective and the perspective of a good society. The enhancement of bodily growth is a controversial objective of any medical therapy or research, especially as long as no physiological causes of limited growth have been discovered. After all, in a normal and healthy population there will always be persons with extremely short stature (and, for that matter, there will be persons with extremely long stature as well).

Interventions are appropriate if their ultimate goal is not just to enhance growth as such, but rather to *reduce the risks of psychological and social problems*. Growth hormone therapy may be part of the medical strategy to reduce these risks. If so, it should be accompanied by a careful monitoring of the psychological and social wellbeing of the child, and by psychological counselling.

This shift in treatment objectives also has consequences for medical research programmes. If enhancement of growth is considered as one of the means to protect the patient's social and psychological wellbeing, endocrinological research on hGH therapy should focus on these latter effects, rather than on gaining extra centimetres. Even more importantly, the positive and negative effects on wellbeing of endocrinological interventions should be compared with the effects of other strategies to protect wellbeing. The development and evaluation of strategies for psychological support of very short children deserves more attention.

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